A. 膵　癌　VII. 膵癌の治療
進行・再発膵癌の治療／化学療法

Taxane系薬剤

Activity of Taxanes for advanced and recurrent pancreatic cancer

朴　成和
福冨　晃

Key words　pancreas cancer, paclitaxel, docetaxel

はじめに

切除不能・再発膵癌に対してgemcitabine (GEM)(遠隔転移)または5-fluorouracil(5-FU)+放射線療法(局所進行)が標準的一次治療として確立されているが予後不良である．また，一次治療がfailureした後の二次治療は確立していない．特に腹水が出現した場合には，全身状態が悪化しているため化学療法が施行されることが少なく，更に，様々な対症療法も効果がないため急速に全身状態が悪化することが多い．有効な薬剤が少なく化学療法が効きにくいとされている膵癌に対して，様々な新規抗がん剤が試されている．taxane系薬剤もその一つであり，単剤だけでなく併用療法の臨床試験の結果が報告されている．

1. Taxane系薬剤の特徴

taxane系の薬剤(paclitaxel, docetaxel)は，胃癌，乳癌，肺癌などの様々な癌種に対して有効性を示す．膵癌と同様の消化器系の腺癌である胃癌に対するpaclitaxelの国内後期第II相試験[1]の結果では，210 mg/m²を1日1回投与し，3週間隔で投与を繰り返す方法において奏効割合は全体で23%(25/107)を示し，前化学療法を有する場合でも23%(15/66)と良好な成績が得られている．また，paclitaxelの特徴として，静脈内投与されたpaclitaxelの腹水への移行は良好で，血中濃度に対し1.4倍の濃度を持続するとの報告や，paclitaxel 80 mg/m²を静脈内投与することにより48時間以上にわたり有効血中濃度である0.01 μM以上を維持するとの報告がある．これらの報告から，腹水を有する症例など腹膜転移例に対する効果が期待されている．また，taxane系の薬剤は放射線に最も感受性のあるG2/M期に細胞周期を同期させるため，放射線感受性を高めることが知られており，臨床的にも放射線との相乗効果も期待されている．

2. Paclitaxel少量分割投与法

paclitaxelは3週ごとの投与と，少量分割(毎週)投与の2つの投与法がある．少量分割療法は我が国では保険適用外の用量・用法となるが，それまでの3週ごとに投与を繰り返す方法に比べ，殺細胞効果発現濃度(0.01 μM)の持続時間を延長することから高い抗腫瘍効果が期待できることが示唆される．実際，MD Anderson Cancer CenterのGreenら[2]は，乳癌の術前化学療法としてpaclitaxel少量分割療法80 mg/m²/week×12コースと3週ごと225 mg/m²×4コー

Narikazu Boku, Akira Fukutomi: Division of Gastrointestinal Oncology, Shizuoka Cancer Center　静岡県立静岡がんセンター 消化器内科

0047-1852/06/¥40/頁/JCLS

スに投与の比較試験を実施し，少量分割療法群で有意に高いpathological CRが認められたと報告している．また安全性については，胃癌領域に限らず，卵巣癌，非小細胞肺癌，乳癌においても，3週ごとに投与を繰り返す投与法に比べ，paclitaxelの主な有害事象である血液毒性について，それぞれ少量分割vs 3週ごと投与で，Grade 2以上の貧血が7.1% vs 18.6%，Grade 3以上の顆粒球減少が7.1% vs 32.3%，Grade 2以上の血小板減少が0% vs 15.7%であり，また，非血液毒性については大きな差は認められなかったが，予期しない入院(3回 vs 15回)や，G-CSF使用回数(7回 vs 33回)[いずれも少量分割vs 3週ごと投与]についても少量分割療法にて少なかったと報告されており，認容性において優れていると考えられる．

3. 膵癌に対するtaxane系薬剤の臨床試験

基礎実験ではtaxane系の薬剤は膵癌細胞に対する効果が示され，臨床でもRougierら[3]はdocetaxelを投与した17例中5例(29%)の奏効を報告したが，他の臨床試験では効果を確認することができなかった[4,5]．同様にpaclitaxelも奏効率0-8%[6,7]と，膵癌に対するtaxane系薬剤の際立った有効性を示唆するものはない．また，GEMとdocetaxelの併用が報告されているが，奏効率は6-13%[8,9]であった．このように，肝転移やリンパ節転移などの測定可能な転移性病変を標的とした第II相試験では，paclitaxel，docetaxelともに，単剤での腫瘍縮小効果およびGEMとの併用での上乗せ効果が小さく，日常診療で膵癌に対してtaxane系の薬剤が用いられることは少ない．

4. 膵癌腹水症例に対するweekly Taxol療法

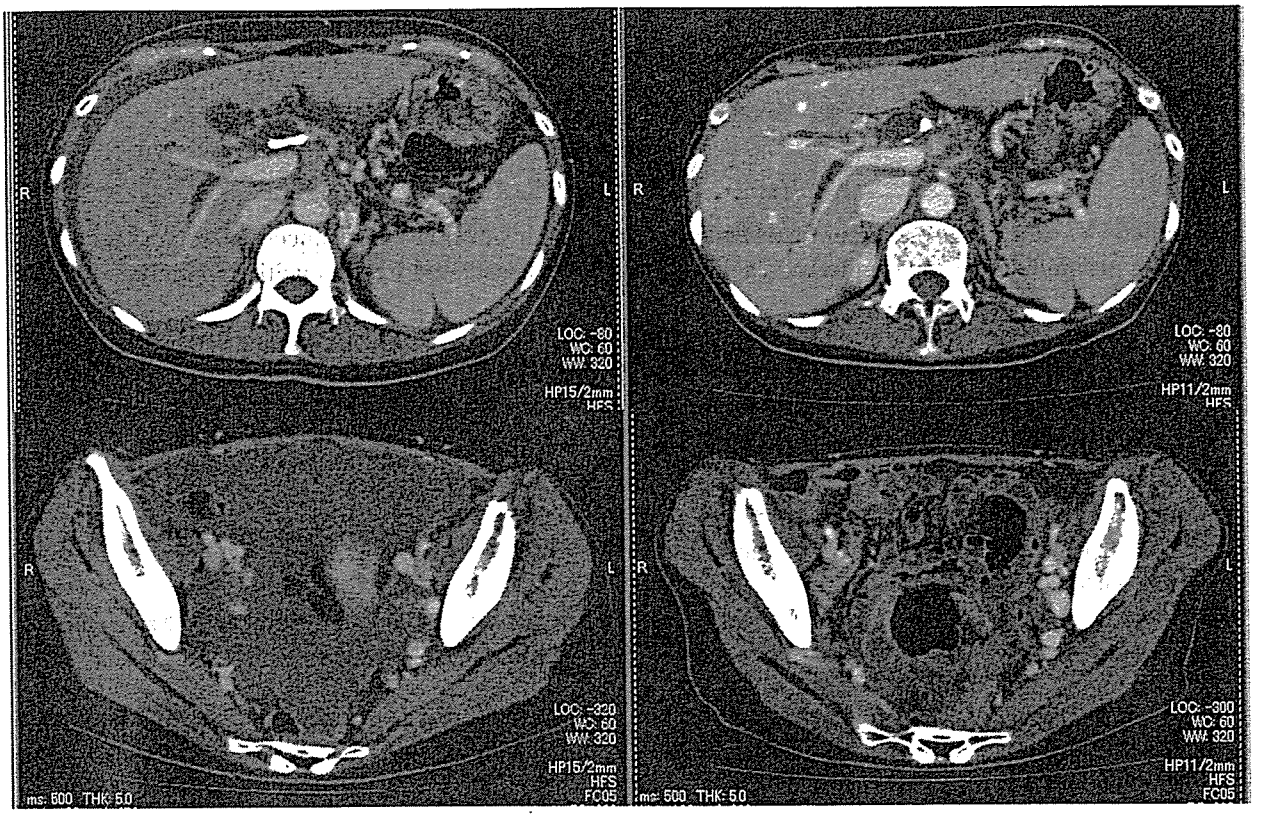
paclitaxelは腹水への移行が良好であり，進行胃癌に対する二次化学療法としてのpaclitaxel少量分割療法で，対象症例数は少ないが腹水の減少効果を40%に認めると報告されている．著者らは，GEMによる一次治療後に増悪し，画像上腹水を有する11例にweekly Taxol療法(80 mg/m²/週，3投1休)を施行した．うち4例(36%)で腹水が減少し(**図1**)，paclitaxel投与開始からの生存期間の中央値は107日であった(**図2**)．腹水を有する膵癌症例は状態が不良なことが多く，予後も極めて悪いことから考えると，腹水を有する膵癌症例に対するpaclitaxelの有効性の可能性を示唆する結果であった．上記の成績は症例数も少なく，retrospectiveな検討であるため，信頼性に乏しいが，paclitaxelの特性を生かした新たな治療戦略の可能性を示唆するものであると考える．しかし，全身状態不良な症例では早期死亡もみられており，注意を要する．

5. Taxane系薬剤を用いた放射線化学療法

Safranら[10]はpaclitaxelと放射線50.4 Gy(1.8 Gy×18回)併用の第I相試験を行い，paclitaxel 50 mg/m²毎週投与を推奨用量としたが，奏効率33%(n=18)，progressive diseaseは1例(6%)のみであったと報告している．本試験を受けてRadiation Therapy Oncology Group(RTOG)[11]では同治療の第II相試験(n=109，RTOG-98-12)を行い，生存期間の中央値11.2カ月，1年および2年生存率はそれぞれ43%，13%と比較的良好な結果を示した．また，paclitaxel+GEM+放射線治療の第I相試験では，GEM 75 mg/m²/week，paclitaxel 40 mg/m²/week+放射線治療50.4 Gyが推奨用量とされ，この第I相試験で1例のpathological CRが得られた．更に，この放射線化学療法をベースにして，その後にfarnesyl transferase inhibitor(R115777)を併用するしないの無作為化第II相比較試験(RTOG PA-0020)が行われ，登録が終了した．現在の局所進行膵癌に対する放射線化学療法の標準的治療は5-FU+放射線療法であるが，このようにpaclitaxelの放射線増感効果も期待されている．

おわりに

膵癌に対するtaxane系薬剤は，これまでの第



a. GEM failure 後腹水出現　　**b.** paclitaxel にて腹水減少

図1　二次治療以降としての paclitaxel にて腹水が減少した症例

II相試験の結果では測定可能な評価病変における腫瘍縮小効果は小さく，膵癌に対して active な薬剤であるとはいえない．一方，これらの薬剤は上記のように腹水症例に対する有効性や良好な放射線感受性増加作用などの特徴を有しているが，局所進行膵癌の原発巣や腹水に対する有効性は通常の第II相臨床試験では評価が難しい．しかし，第II相臨床試験の結果では奏効率が高いとはいえない GEM は 5-FU との第III相比較試験において，疼痛，performance status，体重をからめた clinical benefit response を primary endpoint として優越性が証明された．膵癌では腫瘍縮小効果が得られにくいため，新たな治療法の開発のためには，第II相試験における測定可能な評価病変での腫瘍縮小効果だけでなく，それぞれの薬剤の長所，特徴をとらえた評価が必要であろう．taxane 系薬剤の膵癌に対する効果も，腹膜転移に対する有効性や放射線増感作用などの特徴を明らかにするために，何らかの clinical benefit をみることができる primary endpoint を設定した臨床試験を行い，再評価する必要があると思われる．更には，膵癌と同様に腹膜転移の頻度が高い胃癌においては，消化管通過障害や腹水を有する腹膜転移優位の症例を，肝転移などが優位である症例と別集団として2つの比較試験を展開し，それぞれの治療戦略を構築しようとしている．膵癌において

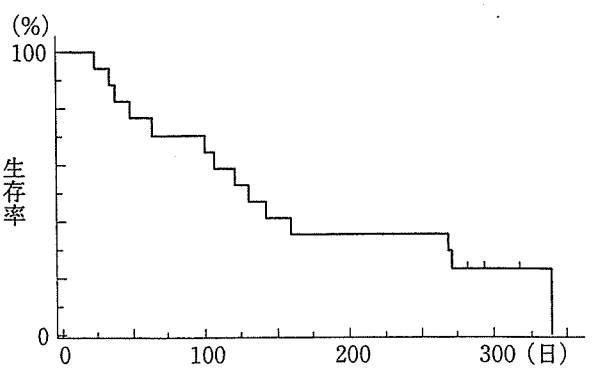


図2　二次治療以降として paclitaxel が投与された腹水を有する膵癌症例の生存曲線(n=11)

も，極めて小さなうちから遠隔転移を有する症例と，局所進行膵癌のように腹膜転移優位な臨床経過をたどる症例がある．今後，taxane系薬剤を含めた新規抗がん剤において，tumor behaviorに合わせた治療戦略を構築していく必要があると思われる．

文　献

1) Yamada Y, et al: Phase 2 trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol **12**: 1133, 2001.
2) Green MC, et al: Weekly Paclitaxel(P) Followed by FAC in the Neo-Adjuvant Setting Provides Improved Pathologic Complete Remission(PCR) Rates Compared to Standard Paclitaxel Followed by FAC Therapy-Preliminary Results of an Ongoing Prospective Randomized Trial. Proc ASCO, 129, 2001.
3) Rougier P, et al: A phase II study: docetaxel as first-line chemotherapy for advanced pancreatic adenocarcinoma. Eur J Cancer **36**(8): 1016-1025, 2000.
4) Androulakis N, et al: Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II study. J Clin Oncol **17**(6): 1779-1785, 1999.
5) Okada S, et al: Phase II study of docetaxel in patients with metastatic pancreatic cancer: a Japanese cooperative study. Cooperative Group of Docetaxel for Pancreatic Cancer in Japan. Br J Cancer **80**(3-4): 438-443, 1999.
6) Gebbia N, Gebbia V: Single agent paclitaxel in the treatment of unresectable and/or metastatic pancreatic adenocarcinoma. Eur J Cancer **32A**(10): 1822-1823, 1996.
7) Whitehead RP, et al: Phase II trial of paclitaxel and granulocyte colony-stimulating factor in patients with pancreatic carcinoma: a Southwest Oncology Group study. J Clin Oncol **15**(6): 2414-2419, 1997.
8) Cascinu S, et al: A phase I-II study of gemcitabine and docetaxel in advanced pancreatic cancer: a report from the Italian Group for the Study of Digestive Tract Cancer(GISCAD). Ann Oncol **10**(11): 1377-1379, 1999.
9) Stathopoulos GP, et al: Treatment of pancreatic cancer with a combination of docetaxel, gemcitabine and granulocyte colony-stimulating factor: a phase II study of the Greek Cooperative Group for Pancreatic Cancer. Ann Oncol **12**(1): 101-103, 2001.
10) Safran H, et al: Paclitaxel and concurrent radiation for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys **49**(5): 1275-1279, 2001.
11) Rich T, et al: Phase II study of external irradiation and weekly paclitaxel for nonmetastatic, unresectable pancreatic cancer: RTOG-98-12. Am J Clin Oncol **27**(1): 51-56, 2004.

症 例

S-1単剤療法が奏効した肝転移を有する進行膵癌の1例

吉野 孝之 福冨 晃 朴 成和*

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Chemotherapy-naïve Advanced Pancreatic Cancer with Multiple Liver Metastases Successfully Treated by S-1 Monotherapy—A Case Report: Takayuki Yoshino, Akira Fukutomi and Narikazu Boku (*Division of Gastrointestinal Oncology and Endoscopy, Shizuoka Cancer Center*)

Summary

We report a patient with chemotherapy-naïve advanced pancreatic cancer having multiple liver metastases which dramatically responded to S-1, an oral fluoropyrimidine. The patient was enrolled in the "Late Phase II Clinical Study of S-1 in Patients with Advanced Pancreatic Cancer." Anti-tumor efficacy after the first four courses of S-1 monotherapy was confirmed to be partial response (PR) in overall response by Response Evaluation Criteria in Solid Tumors (RECIST). Grade 3 neutropenia was observed, but no other severe toxicities were noted. On the basis of the results of the late phase II clinical study, S-1 is a promising agent for systemic chemotherapy against advanced pancreatic cancers because of its excellent efficacy, high tolerability, and convenient route of oral administration. Key words: S-1, Late phase II clinical study, Advanced pancreatic cancer, Liver metastasis, Monotherapy (*Received Aug. 17, 2006/Accepted Aug. 31, 2006*)

要旨 肝転移を有する進行膵癌患者に経口フッ化ピリミジン系抗癌剤のS-1を投与し，優れた抗腫瘍効果を認めた1例を経験した。本症例は，「進行膵癌患者におけるS-1の後期臨床第II相試験」の登録症例で4コースまでの抗腫瘍効果は，測定可能病変である肝転移巣はPR，評価可能病変の原発巣はNC，総合評価はPR判定であった。副作用については好中球数減少(grade 3)を認めたが，その他はいずれも軽微であった。S-1は後期臨床第II相試験の治療成績から進行膵癌の全身化学療法において有効かつ忍容性に優れ，さらに経口投与である利便性から今後期待される薬剤である。

はじめに

膵癌は早期診断が極めて困難な難治性癌であり，他の消化器癌と比較して悪性度が高く予後不良である。リンパ節転移および主要血管（上腸間膜動・静脈，門脈，脾静脈，腹腔動脈など），後腹膜神経叢への浸潤を来しやすいため[1]，一般に切除率は低率である。欧米の膵癌症例の集計結果では，切除率は10%以下と極めて低く，わが国の最近の膵癌全国登録調査報告[2]によると，切除例は1,457例中574例（39.4%）と欧米と比較して高いものの，その大半は発見時切除不能である。切除不能または術後再発膵癌に対して全身化学療法が行われているが，本邦ではgemcitabine (GEM) しかなく[3]，他の有効な薬剤の開発が急務である。経口フッ化ピリミジン系抗癌剤であるS-1はいくつかの臨床試験[4]において，切除不能進行膵癌に対し高い抗腫瘍効果と安全性が示されており，今後期待される薬剤である。測定可能な転移巣を有する膵癌患者を対象に実施した，S-1単剤療法の後期臨床第II相試験の登録症例で著明な奏効を認めた1症例を報告する。

I. 治療法

S-1の初回投与量は，患者の体表面積(m^2)に合わせ1回量を1.25 m^2未満の場合は40 mg/回，1.25 m^2以上～1.50 m^2未満の場合は50 mg/回，1.50 m^2以上の場合は60 mg/回とし，朝夕食後の1日2回，28日間連日経口投与し，その後14日間の休薬をもって1コースとする[5]。忍容し難い有害事象が生じた場合は，投与量を1段階下げて投与を再開する。減量後に忍容し難い有害事象を再度認めた場合は，投与期間の短縮を行う。患者からの同意撤回がなければ病態進行(PD，臨床症状の悪化を含む)まで治療を継続する。

連絡先: 〒411-8777 静岡県駿東郡長泉町下長窪1007 * 静岡県立静岡がんセンター・消化器内科
吉野 孝之

0385-0684/06/¥500/論文/JCLS

II. 症　例

症例: 60歳代，女性。身長153 cm，体重50.8 kg，体表面積1.427 m²，Karnofsky performance status（KPS）100%。

臨床診断: 膵癌，傍大動脈周囲リンパ節転移，多発肝転移。

組織型: 管状腺癌。

合併症: なし。

既往歴: 急性肝炎。

前治療: なし。

併用薬: ロキソプロフェンナトリウム，レバミピド，トリアゾラム，塩酸ロペラミド，ピレノキシン，フラビンアデニンジヌクレオチドナトリウム，ヒアルロン酸ナトリウム。

併用療法: なし。

血液検査所見: S-1投与開始前（治療直前）の血液検査データは，Hb 11.8 g/dl，WBC 4,220/μl（好中球76.1%），Plt 15.4×10⁴/l，T-Bil 1.0 mg/dl，AST 15 IU/l，ALT 11 IU/l，ALP 292 IU/l，Alb 4.0 g/dl，Cr 0.59 mg/dl と良好であった。

治療経過: 2003年7月30日よりS-1 50 mg/回×2/日で28日間単剤による投与を開始した。1コース目で安全性に問題がなかったことから，休薬期間を短縮し，9月3日より2コース目を開始，休薬を7日に短縮するとともにS-1の投与量を増量し，60 mg/回×2/日で28日間継続投与し，7日間休薬する投与法で5コースまで投薬を行った。治療効果については原発巣は傍大動脈リンパ節と一塊となり，その境界が不明瞭なため測定不能と評価した。標的病巣として肝臓の治療前のCT所見（図1a）より1コース後の縮小率は31.6%，2コース後では73.4%（PR）と著明な縮小効果を認め，3コース後では87.3%，4コース後では92.8%とPR継続であった（図1b）。これらの肝転移巣の評価から4コースまでの抗腫瘍効果は，評価可能病変である肝転移巣はPR，評価可能病変の原発巣はNC，総合評価はPRであった。CA 19-9は登録前707 U/ml，1コース開始直後1,242 U/ml と異常高値を示したものの，1コース終了時点では336 U/ml に低下し，3コース目終了時には22 U/ml と基準値以下に改善した（図2）。

grade 3以上の副作用に関しては，3コースにおいて好中球数減少を認めたのみであった。KPSは4コース終了時点においても100%であった。

その後，2003年12月17日から5コース目開始，2004年1月20日のCT所見にて右副腎，肝に新病変の出現で病態の明らかな進行（PD）と判断した。2004年1月27日

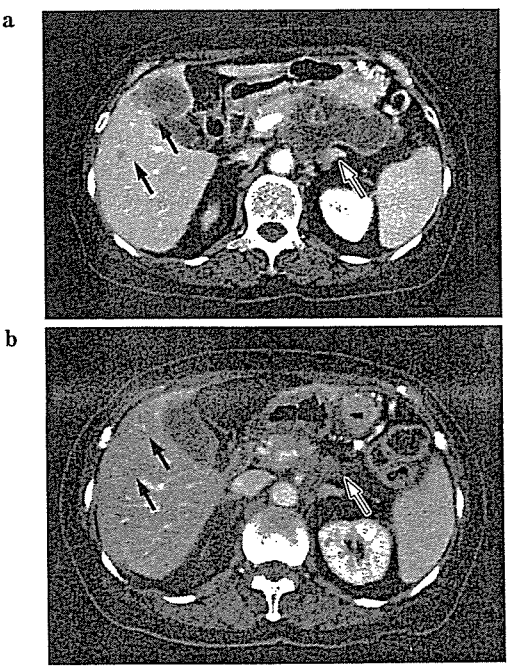

図 1
a: 治療前のCT所見，b: S-1 4コース終了後のCT所見
原発巣（白矢印），肝転移巣（黒矢印）。
原発巣の著明な縮小と肝転移巣の消失を認める（総合評価はPR）。

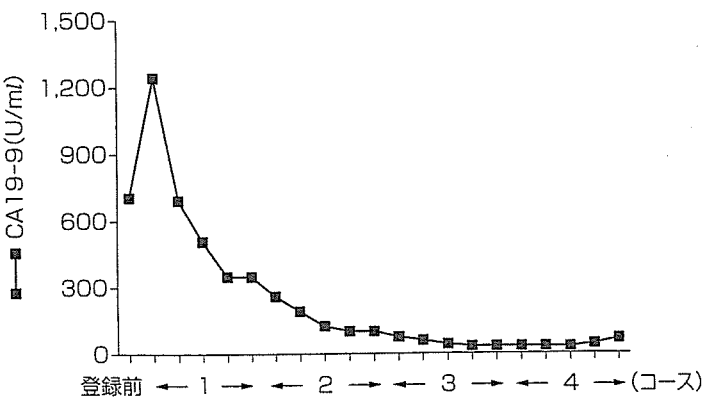

図 2 腫瘍マーカーの推移

より二次治療としてGEM療法を開始し，PDが確認された2004年6月22日まで治療を継続した。最良腫瘍縮小効果は不変（SD）であった。その後は緩和治療となり2004年9月5日に原病死した。全経過は1年2か月であった。

III. 考　察

S-1単独投与で著明な奏効を認めた多発肝転移を有する進行膵癌症例を経験した。従来，5-FU系薬剤は奏効率が低く，その上消化管毒性による重篤な下痢や口内炎などの有害事象を認めてきた。経口フッ化ピリミジン系抗癌剤S-1は，強力な5-FUの分解抑制作用を有するギメラシル（CDHP）および消化管毒性軽減のモジュレーターとして見いだされたオテラシルカリウム（Oxo）と5-FUのプロドラッグであるテガフール（FT）とを配合した薬剤であり，高い抗腫瘍効果と安全性，特に消化管毒性による有害事象発現の抑制効果が期待されている[6]。5-FUは，ジヒドロピリミジンデヒドロゲナーゼ（DPD）により分解され不活性となり，肝においてDPDで分解されるとされてきた。しかし近年，膵癌などの癌組織においてもDPDが発現していることが判明し[7]，腫瘍組織自体における5-FUの抗腫瘍効果の減弱化が指摘されている。S-1は基礎実験においては，種々の癌に対する静注5-FUや経口UFTと比較し高い抗腫瘍活性が実証されており[8]，臨床第II相試験が実施されることとなった[4]。前期臨床第II相試験では，19例中4例がPR（21.1%）と判定され，生存期間中央値は5.6か月で有害事象はその多くが一過性で軽微であった。

後期臨床第II相試験は，無治療の進行膵癌患者を対象（7施設，40例）に，S-1単独投与の有効性と安全性を目的に実施され，40例中PR 15例，NC 11例，PD 13例，評価不能1例で奏効率は37.5%（95%信頼区間：22.7～54.2%），生存期間中央値8.8か月（7.5～10.8か月）の良好な成績が得られている[9]。また，症状緩和効果の評価可能な10例中4例（40%）で改善を認め，grade 3～4の有害事象は食欲不振（12.5%），下痢（7.5%），悪心（7.5%），好中球数減少（7.5%）が主で，その他はいずれも軽微であった[9]。本症例も，3コースにおいて好中球数減少（grade 3）を認めるのみで忍容性は良好であった。

切除不能進行膵癌を対象に，当時の標準治療である5-FU療法に試験治療であるGEM療法を比較した臨床第III相試験で，5-FU群と比較しGEM群のほうが症状緩和効果が4.8%，23.8%と有意に高く，生存期間中央値も4.4か月，5.7か月と有意に優れていると報告されている[10]。今回，S-1後期臨床第II相試験で症状緩和効果は改善し，生存期間中央値も良好な成績が報告されたが，今後適切な比較試験によって膵癌におけるS-1の位置付けを明らかにすることは重要な課題である。

現在，「科学的根拠に基づく膵癌診療ガイドライン2006年版」では，エビデンスに基づき遠隔転移を有する膵癌に対する一次化学療法として，GEMが推奨されている[3]。一方，切除不能例に対する二次化学療法は推奨される根拠に乏しく，臨床試験において行われるべきとされているが，S-1の後期臨床第II相試験の成績から，S-1はGEM不応例に対する二次治療として，一次治療としてのGEMとS-1の併用療法も期待される。また，S-1は単剤でも高い抗腫瘍効果と安全性を示すことから，進行膵癌症例に対する一次療法としても症状の緩和効果や経口投与の利便性の面からも期待される薬剤である。

文　献

1) 松野正紀，窪田敬一：膵癌2．外科．臨床腫瘍学（西條長宏・編），癌と化学療法社，東京，2003，pp 717-722.
2) 松野正紀：膵癌全国登録調査報告（1999年度症例の要約）．膵臓 **16**: 115-147, 2001.
3) 日本膵臓学会膵癌診療ガイドライン作成小委員会・編：CQ 2 化学療法．科学的根拠に基づく膵癌診療ガイドライン．金原出版，東京，2006，pp 29-42.
4) Ueno H, Okusaka T, Ikeda M, *et al*: A phase II study of S-1 in patients with metastatic pancreatic cancer. *Oncology* **68**: 171-178, 2005.
5) 坂田　優：消化器癌化学療法の現況：Introductionと総論：消化器癌の外来化学療法消化器病セミナー98（田村和夫・編），へるす出版，東京，2005，pp 1-17.
6) Tatsumi K, Fukushima M, Shirasaka T, *et al*: Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res* **78**: 748-755, 1987.
7) Fukushima M, Morita M, Ikeda K, *et al*: Population study of expression of thymidylated synthase and dihydropyrimidine dehydrogenase in patients with solid tumors. *Int J Mol Med* **12**: 839-844, 2003.
8) Shirasaka T, Shimamoto Y, Ohshimo H, *et al*: Development of a novel form an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* **7**: 548-557, 1996.
9) 奥坂拓志，船越顕博，古瀬純司・他：進行膵癌患者におけるS-1後期臨床第II相試験―多施設共同試験の成績―．日癌治療会誌（第43回日本癌治療学会総会抄録号）**40**(2): 391, 2005.
10) Burris HA 3rd, Moore MJ, Andersen J, *et al*: Improvements in survival and clinical benefit with gemcitabine as first line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* **15**(6): 2403-2413, 1997.

Review

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International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas

Masao Tanaka[a] Suresh Chari[b] Volkan Adsay[c]
Carlos Fernandez-del Castillo[d] Massimo Falconi[e] Michio Shimizu[f]
Koji Yamaguchi[a] Kenji Yamao[g] Seiki Matsuno[h]

[a]Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [b]Department of Gastroenterology, Mayo Clinic, Rochester, Minn., USA; [c]Department of Pathology, Wayne State University and The Karmanos Cancer Center, Harper Hospital, Detroit, Mich., USA; [d]Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Mass., USA; [e]Department of Surgery, Verona University, Verona, Italy; [f]Department of Pathology, Saitama Medical School, Saitama, Japan; [g]Department of Gastroenterology, Aichi Cancer Center, Nagoya, Japan, and [h]Department of Gastroenterological Surgery, Graduate School of Medicine, Tohoku University, Sendai, Japan

Key Words
Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Guidelines for management of IPMN/MCN · Pancreatic neoplasm · Pancreatectomy

Abstract
Non-inflammatory cystic lesions of the pancreas are increasingly recognized. Two distinct entities have been defined, i.e., intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). Ovarian-type stroma has been proposed as a requisite to distinguish MCN from IPMN. Some other distinct features to characterize IPMN and MCN have been identified, but there remain ambiguities between the two diseases. In view of the increasing frequency with which these neoplasms are being diagnosed worldwide, it would be helpful for physicians managing patients with cystic neoplasms of the pancreas to have guidelines for the diagnosis and treatment of IPMN and MCN. The proposed guidelines represent a consensus of the working group of the International Association of Pancreatology.

Masao Tanaka chaired the working group and Suresh Chari served as a co-chair. They and the following six authors listed in alphabetical order equally contributed to preparation of the guidelines. Seiki Matsuno selected the members of the working group, planned and realized the consensus meeting and critically edited the manuscript.

Introduction

Non-inflammatory cystic lesions of the pancreas are more common than previously recognized. In an autopsy study [1], small cystic lesions were found in nearly half of the 300 patients studied, the prevalence increasing with age. While most cysts were non-neoplastic, 3.4% of the patients had cysts that showed epithelial atypia [1]. It is therefore not surprising that with the increasing use of high-resolution abdominal imaging techniques, cystic

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Masao Tanaka, MD, PhD, FACS
Department of Surgery and Oncology
Graduate School of Medical Sciences, Kyushu University
Fukuoka 812-8582 (Japan)
Tel. +81 92 642 5437, Fax +81 92 642 5457, E-Mail masaotan@med.kyushu-u.ac.jp

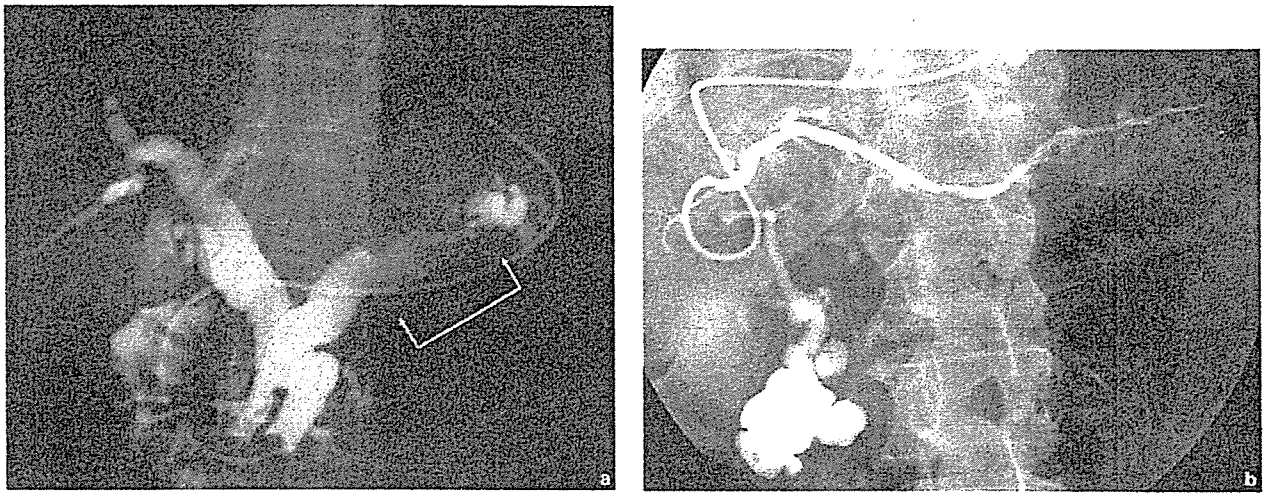

Fig. 1. Pancreatograms using a balloon catheter retained by ERCP showing a main duct IPMN (**a**) with mural nodules (arrow) and a branch duct IPMN in the head of the pancreas with clear communication with the pancreatic duct (**b**).

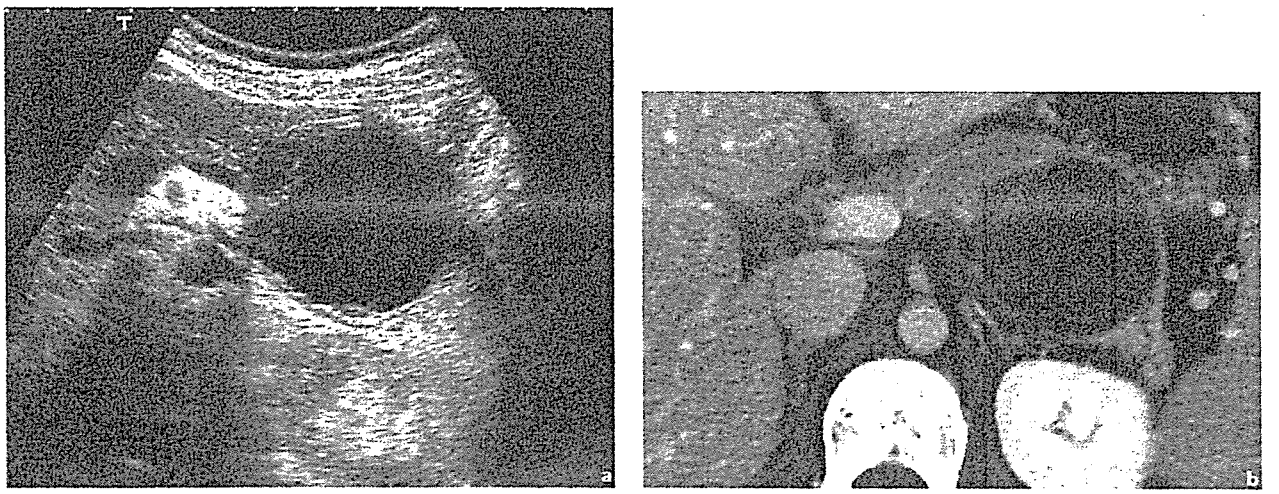

Fig. 2. Ultrasonogram (**a**) and computed tomogram (**b**) demonstrating an MCN.

neoplasms of the pancreas are being increasingly identified, often as incidental findings [2].

In 1996, the World Health Organization (WHO) classified cystic mucin-producing pancreatic neoplasms into two distinct entities [3], i.e., intraductal papillary mucinous tumor and mucinous cystic tumor. In the revised WHO classification in 2000 [4], the two neoplasms were renamed as intraductal papillary mucinous neoplasm (IPMN) (fig. 1) and mucinous cystic neoplasm (MCN) (fig. 2), respectively. Since then much has been learnt about the clinical, radiographic, and histological characteristics of these neoplasms. For example, the presence of ovarian-type stroma has been proposed as a characteristic feature of MCN that distinguishes it from IPMN. While there have been rapid advances in our understanding of the prevalence of cancer at diagnosis and the risk of recurrence following resection, there are still considerable gaps in our knowledge of the natural history of these neo-

Table 1. List of clinical questions

1. Definition and Classification
1a. It has been suggested that IPMNs arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?
1b. In most IPMNs there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNs be considered as advanced branch duct IPMNs?
1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?
1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?
2. Preoperative evaluation
2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?
2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?
3. Indication for resection
3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
3b. Should all branch duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
4. Method of resection
4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?
4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?
4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?
5. Histological questions
5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?
5b. Are there special instructions for specimen processing in MCNs and IPMNs?
5c. Are there special instructions for specimen processing to differentiate branch duct IPMNs from main duct IPMNs?
6. Method of follow-up
6a. How should patients with non-resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?

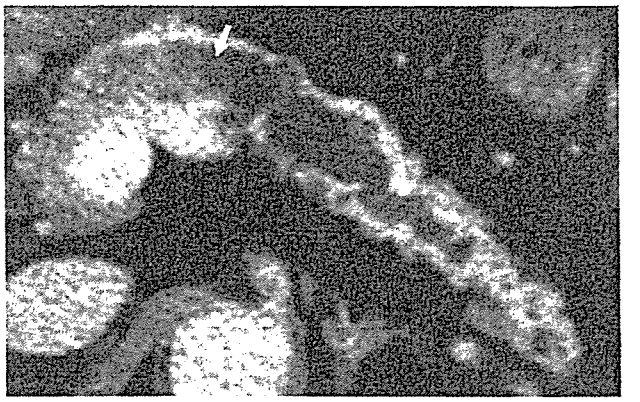

Fig. 3. Computed tomogram showing a markedly dilated main pancreatic duct in a patient with a main duct IPMN with a mural nodule in the body of the pancreas (arrow).

plasms. However, in view of the increasing frequency with which these neoplasms are being diagnosed worldwide, it would be helpful for physicians managing patients with cystic neoplasms of the pancreas to have guidelines for the diagnosis and treatment of IPMN and MCN. No doubt, as our understanding grows, these guidelines will need revision.

During the Eleventh Congress of the International Association of Pancreatology held in Sendai, Japan, from July 11 through 14, 2004, we had a consensus meeting on this topic. The working group set up 6 clinical questions with 18 subdivisions (table 1), and continued to work on the answers. The proposed guidelines represent a consensus of the working group of the International Association of Pancreatology at this moment.

1. Definition and Classification

1. It has been suggested that IPMN arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?

IPMN can be classified as main duct IPMN or branch duct IPMN based on imaging studies or by histology [5]. On conventional imaging (i.e., computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP)), dilation of the main duct ≥1 cm strongly suggests main duct IPMN (fig. 3), whereas a presence of a pancreatic mucinous cyst communicating with the pancreatic duct without main duct dilation suggests branch

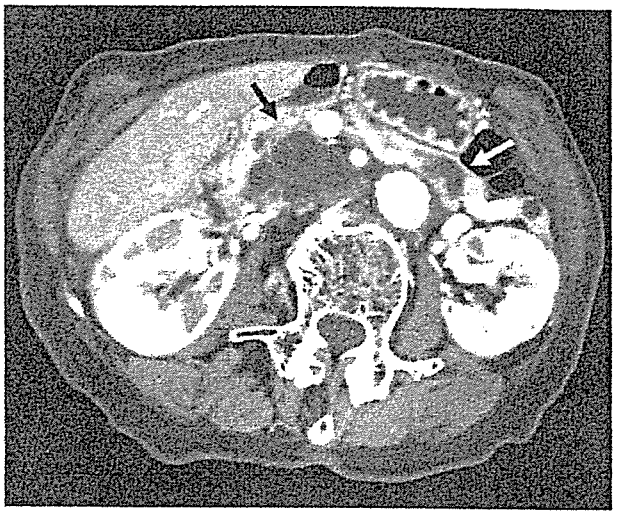

Fig. 4. Computed tomogram demonstrating a multilocular cystic lesion in the head of the pancreas (black arrow) and a unilocular cyst in the tail (white arrow), representing multiple branch duct IPMNs.

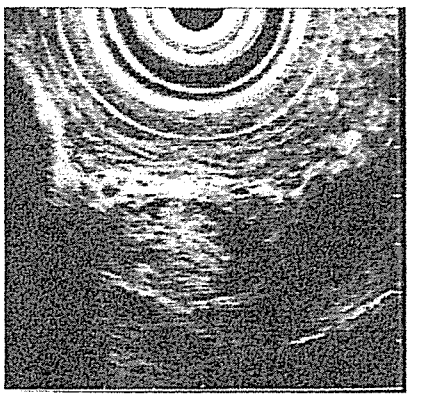

Fig. 5. Endosonogram demonstrating a mural nodule in a branch duct IPMN in the head of the pancreas.

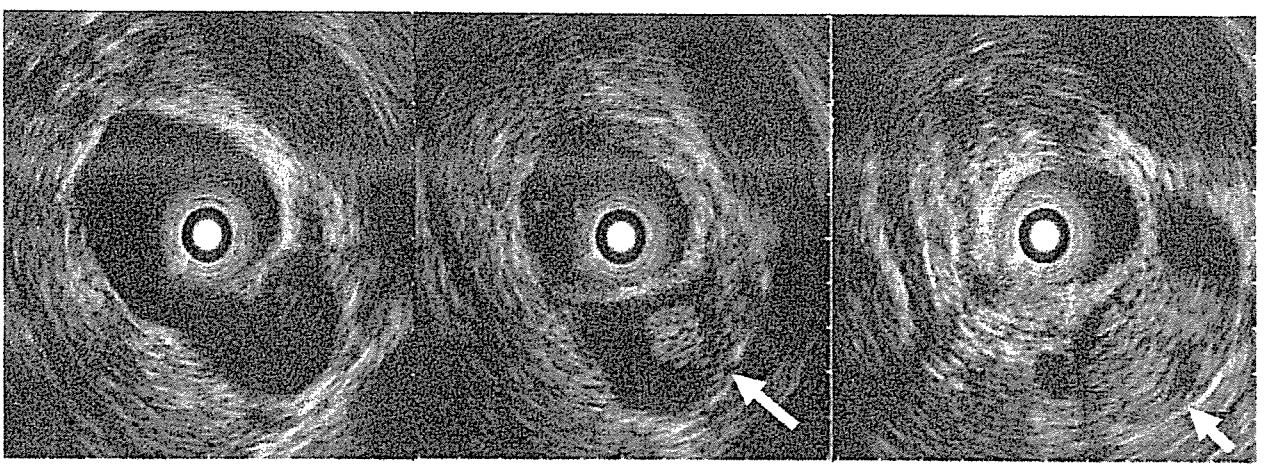

Fig. 6. Intraductal ultrasonogram visualizing a mural nodule in a branch duct IPMN in the head of the pancreas (arrows).

duct IPMN (fig. 4) [6–8]. The presence of the papillary growth in branch or main ducts can be ascertained with greater degree of certainty using more sophisticated and invasive imaging studies, such as endoscopic ultrasonography (EUS) (fig. 5) [9, 10], endoscopic retrograde cholangiopancreatography (ERCP) with or without the use of a balloon catheter (fig. 1a, b), intraductal ultrasonography (fig. 6) [11, 12] and peroral pancreatoscopy (fig. 7) [13, 14], or by a combination of intraductal ultrasonography and peroral pancreatoscopy [15]. However, these techniques are not widely available. The most definitive classification of IPMN into main or branch duct type is made by histology, provided the resected specimen is properly sectioned.

Table 2. Malignancy in main duct IPMNs (including the mixed type IPMN)

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	13	92	23
Terris [17]	2000	30	57	37
Doi [18]	2002	12	83	Not stated
Matsumoto [19]	2003	27	63	Not stated
Choi [20]	2003	34	85	Not stated
Kitagawa [21]	2003	37	65	54
Sugiyama [22]	2003	30	70	57
Sohn [23]	2004	69	Not stated	45
Salvia [24]	2004	140	60	42
Mean of all series			70	43

Table 3. Malignancy in branch duct IPMNs

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	17	31	6
Terris [17]	2000	13	15	0
Doi [18]	2002	26	46	Not stated
Matsumoto [19]	2003	16	6	Not stated
Choi [20]	2003	12	25	Not stated
Kitagawa [21]	2003	26	35	31
Sugiyama [22]	2003	32	40	9
Sohn [23]	2004	60	Not stated	30
Mean of all series			25	15

Main duct IPMN and branch duct IPMN have significant differences in prevalence of cancer ranging from 57 to 92% [16–24] and 6 to 46% [16–23], respectively (tables 2, 3) and therefore the classification has prognostic implications. In practice, patients classified as branch duct IPMN based on preoperative imaging studies sometimes show microscopic involvement of the main duct not detectable preoperatively. It is unclear if such subjects with 'predominantly' branch duct IPMN with microscopic main duct involvement have a higher prevalence of malignancy compared to those with dysplasia confined solely to the branch duct.

1b. In most IPMNS there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNS be considered as advanced branch duct IPMNS?

The categorization of IPMN according to the differential involvement of the branch vs. main duct is mostly based on imaging findings, and as such this classification scheme appears to have substantial value in preoperative management algorithms for IPMN. The role of this classification, however, may be overridden once the neoplasm is resected, re-evaluated pathologically, and graded as adenoma, borderline, CIS or invasive. On the other hand, there are significant pathologic correlates of this classification: IPMNs categorized as 'branch type' by radiographic methods are typically found to be smaller, less complex (less papillary), and non-malignant (more commonly adenomas with gastric/foveolar type epithelium), which explains why many branch duct IPMNs have been successfully managed by conservative therapy, even 'wait and watch'.

One pitfall in this classification scheme, however, is that many of the branch duct IPMNs prove, by microscopic examinations, to have some degree of involvement in the main duct as well. Therefore, predominantly main duct type and predominantly branch duct type may be a more accurate conceptualization of these categories, al-

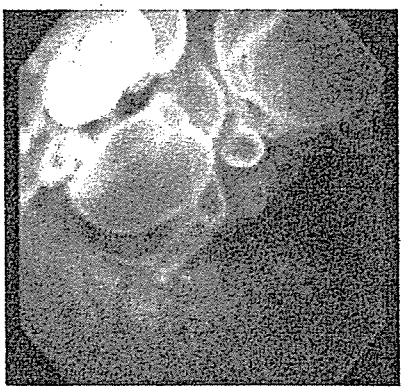

Fig. 7. Fish egg-like appearance of a main duct IPMN by peroral pancreatoscopy.

though the word predominantly is omitted for practical purposes. In fact, 'branch limited' vs. 'beyond the branch' may be even more accurate. On the other hand, there are more important and practical implications of this conceptual issue. First, it is difficult to determine how much of the main duct involvement is necessary to qualify the lesion as 'main duct IPMN'. In this regard, more clinical follow-up data need to accumulate before the criteria for this distinction can be established. In the meantime, however, the criteria advocated for the definition of IPMN in the recent international consensus manuscript [25] may be applicable for practical purposes. Even when these criteria are applied, however, many IPMNs would still fall into a mixed category. Therefore, it is necessary to retain this mixed category until future studies further clarify the criteria to distinguish these two groups.

Since clinicopathologic correlation is imperative in the management of IPMNs as well as in understanding the biologic behavior of the subsets of this type of neoplasm, it is recommended that surgical pathologists make every attempt to determine branch vs. main duct type, if nothing else, in order to provide verification to this clinical classification. For this purpose, the findings regarding the distribution of ductal involvement may be communicated in a note or comment following the main diagnosis in the surgical pathology report.

1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?

The most characteristic histological finding in MCN is the presence of a unique ovarian-type stroma (fig. 8) [26] not found in other pancreatic neoplasms. This ovarian-

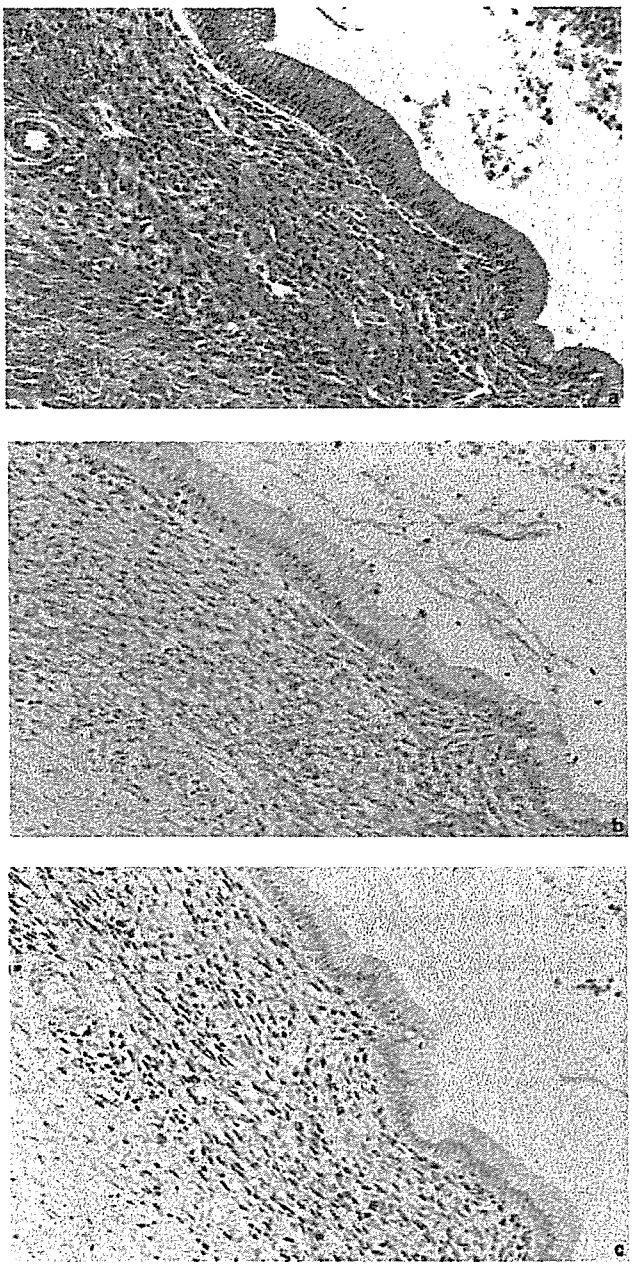

Fig. 8. Ovarian-type stroma in a mucinous cystic neoplasm. Hematoxylin and eosin staining (**a**) and immunohistochemical staining of estrogen receptor (**b**) and progesterone receptor (**c**). ×200.

type stroma forms a layer of variable thickness beneath the epithelial lining. The stromal cells have oval nuclei and spindled cytoplasm, and are arranged in long fascicles. The resemblance to ovarian stroma is further

strengthened by the presence of occasional 'lutenized' cells – epithelioid cells with abundant clear cytoplasm. A study of 34 pancreatic MCN and 10 ovarian MCN showed the ovarian stroma of MCN from the two organs shared the same immunohistochemical and histological characteristics [27].

Like its ovarian counterpart, the stroma of pancreatic MCN variably stains for estrogen and progesterone receptors (fig. 8b,c), with 61.8% of pancreatic MCN staining for human chorionic gonadotropin [27].

The most important question with regard to the accurate classification of MCN and its differentiation from branch duct form of IPMN is whether the presence of ovarian-type stroma is required to diagnose MCN. Three studies on MCN have used ovarian-type stroma as a requisite criterion for diagnosis of MCN [28–30]. When defined by the presence of ovarian-type stroma, MCN has a distinct demographic profile; it occurs almost exclusively in women and is almost always found in the pancreatic body/tail region [28, 29]. It has been argued that theoretically it may be possible that postmenopausal women and men with MCN may fail to demonstrate ovarian-type stroma. In a study of 56 MCN defined strictly by presence of ovarian stroma, 9 patients (16%) were >60 years of age [28]. Also, there are male patients with mucinous cystadenoma with ovarian-type stroma [28, 31].

In the absence of a definitive marker, other than ovarian-type stroma, to distinguish MCN from IPMN, it is currently impossible to say if neoplasms classified on the basis of any criterion other than presence of ovarian-type stroma (for example, non-communication with the duct) are indeed MCN. It has become clear over the past few years that making exceptions to the ovarian-type stroma rule frequently leads to misclassification of IPMN as MCN [28]. Therefore the term MCN should be restricted to neoplasms exhibiting ovarian-type stroma.

Clearly, typical MCN with ovarian-type stroma is rare in males and it is less common in postmenopausal women than in women of childbearing age. Occasionally, mucin-producing pancreatic cystic lesions are seen in men or postmenopausal women that neither have ovarian-type stroma nor have typical histological features seen in branch duct IPMNs such as a thin wall, grape-like appearance and a communication with the pancreatic duct. Rather than classify such lesions as MCNs, we propose the use of the term 'indeterminate mucin-producing cystic neoplasm of the pancreas'. In future, when specific markers of IPMN and MCN become available, these lesions may be more definitively classified.

1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?

The general recommendation has been that all mucin-producing neoplasms undergo resection in view of their malignant potential, which questions the clinical utility of careful differentiation of MCN from IPMN [30, 32–34]. However, there are crucial differences between MCN and IPMN with regard to pathogenesis, multifocality, need for follow-up and prevalence of cancer that impact clinical management.

Due to its close histological and immunohistochemical resemblance to ovarian mucinous cystadenomas, MCN has been postulated to arise from ovarian rests in the pancreas [29]. IPMN appears to arise from the pancreatic duct.

MCN and IPMN also have important clinical differences. MCNs are generally solitary and do not recur after complete resection [35, 36]. On the other hand, branch duct IPMNs have been reported to be multifocal in distant regions of the pancreas in up to 30% of patients [37–39], and there is at least a 10% recurrent rate in those patients with non-invasive IPMN who undergo partial pancreatic resection with negative margins [40]. Thus, while no follow-up is needed after resection of non-invasive MCN, young patients with IPMN need follow-up, especially if they have unresected synchronous lesions.

The prevalence of invasive carcinoma reported in MCN has varied widely from 6 to 36% [28–30]. However, data on prevalence of invasive carcinoma in MCN are hard to interpret as few studies have used ovarian-type stroma as a necessary criterion for diagnosis of MCN. Even in studies restricted to neoplasms with ovarian-type stroma the prevalence of cancer has varied from 6 to 27% [28, 29]. In IPMN, prevalence of invasive carcinoma at diagnosis has been reported to be high in main duct IPMN (23–57%, table 2) and lower in branch duct IPMN (0–31%, table 3).

2. Preoperative Evaluation

2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?

There are some obvious differences in clinicopathological features between IPMN and MCN with ovarian-type stroma (table 4) [28–30, 41–47]. Understanding of

Table 4. Typical features of MCN and branch duct IPMN

Characteristic	MCN	Branch duct IPMN
Gender (% female)	>95%	~30%
Age (decade)	4th and 5th	6th and 7th
Location (% body/tail)	95%	~30%
Common capsule	Yes	No
Calcification	Rare, curvilinear, in the wall of cyst	No
Gross appearance	Orange-like	Grape-like
Internal structure	Cysts in cyst	Cyst by cyst
Pancreatic duct communication	Infrequent	Yes (though not always demonstrable)
Main pancreatic duct	Normal or deviated	Normal, or if dilated, suggests combined type

these distinctive features and characteristics of each imaging modality lead to differentiation of the two diseases in most patients. Cystic lesions in males and those in the head of the pancreas are unlikely to be MCN. Magnetic resonance imaging (MRI) with MRCP is the best to outline the gross appearance. Communication with the pancreatic duct demonstrated on imaging studies such as ERCP (most reliable), MRCP (helpful), and EUS (of some help) strongly suggests branch duct IPMN. However, even ERCP in branch duct IPMN may fail to fill the cystic side branch due to mucus plugging the communication. On the other hand, there has been a report of a histologically proven MCN showing communication with pancreatic ducts [47]. In some patients it may therefore be impossible to distinguish between the two entities with certainty preoperatively.

2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?

The Japan Pancreas Society (JPS) defined a non-invasive type of intraductal papillary mucinous carcinoma as limited to the pancreatic duct and a minimally invasive type as having invaded slightly beyond the ductal wall [48]. However, this definition is not so clear. If the minimally invasive intraductal papillary mucinous carcinoma is defined as microscopic cancer invasion to the pancreatic parenchyma, it is impossible to diagnose the minimal invasion preoperatively [49] at present as is the case in minimally invasive MCN.

3. Indication for Resection

3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?

The frequency of malignancy (in situ and invasive) in main duct IPMNs in 8 recent series from Japan, Europe, and the USA has ranged between 60 and 92%, with a mean of 70% [16–24], and approximately two-thirds of these malignant neoplasms have been invasive (table 2). In many studies there has been an attempt to identify radiologic or clinical characteristics that predict malignancy, although unfortunately many of these analyses have been made without separating main duct from branch duct variants. In a series reported by Sugiyama et al. [22], univariate analysis showed that presence of symptoms, a main pancreatic duct diameter >15 mm, and mural nodules were all significant predictors of malignancy in main duct or mixed type IPMNs, although there were patients without nodules or such marked pancreatic duct dilation that had in-situ or invasive carcinoma. The largest published series on main duct IPMNs combines the experiences of the Massachusetts General Hospital and the University of Verona [24]. This study comprised 140 patients, and found that patients with malignant neoplasms were significantly older (by 6.4 years), and had a higher likelihood of presenting with jaundice and/or worsening of diabetes; however, the study also showed that 29% of patients with malignant IPMNs involving the main duct were asymptomatic, and therefore reliance on symptoms could not exclude malignancy. Given the high prevalence of cancer and the data from the reviewed studies it is unlikely that any combination of clinical and radiological

parameters will accurately discriminate between malignant and non-malignant main duct IPMNs. Furthermore, evidence of 'clonal progression' in these neoplasms [50] and the age difference between patients with malignant and benign lesions (which was also shown in another large study) [30] are indicative that most if not all benign main duct IPMNs may progress into invasive cancer, and the long-term follow-up of resected patients shows excellent survival for benign and non-invasive neoplasms and 5-year survival between 36 and 60% for invasive carcinomas [21, 23, 24, 40]. Based on this, our current recommendation is to resect all main duct and mixed variant IPMNs as long as the patient is a good surgical candidate with a reasonable life expectancy. It is important that resections for IPMNs be carried out by surgeons familiar with this diagnosis and in centers where pancreatic surgery can be done safely.

3b. Should all branch duct IPMNs be resected?

Review of 7 recent series describing branch duct IPMNs shows a frequency of malignancy between 6 and 46%, with a mean of 25%, and a frequency of invasive cancer ranging between 0 and 31%, with a mean of 15% (table 3) [16–23]. It is of note that the two studies with the highest frequency of invasive cancer (30 and 31%, respectively) do not describe asymptomatic patients within their series [21, 23], whereas other series with low prevalence of invasive cancer show a significant proportion of incidentally discovered IPMNs [17, 19, 22]. In the series of Sugiyama et al. [22], 53% of branch duct IPMNs were asymptomatic, and none of those patients had invasive cancer. Two studies from Japan have looked at morphologic features of branch duct IPMNs and risk of malignancy. Matsumoto et al. [19] found no malignancy (in situ or invasive) in neoplasms measuring <30 mm and without mural nodules, and described non-operative management in 12 patients with branch duct IPMNs who either refused operation or were at high surgical risk. The majority of these patients were asymptomatic, and had no radiologic progression of their neoplasms during an average follow-up of 33 months. In the second study, Sugiyama et al. [22] found with multivariate analysis that the size >30 mm and presence of mural nodules were the strongest predictors of malignancy in branch duct IPMNs. Only 1/15 patients with a neoplasm <30 mm had in-situ carcinoma (none had invasive cancer), and only 5/22 patients without mural nodules had malignancy. Thus, the overall lower prevalence of malignancy in branch duct IPMNs and the reassurance from the above studies that the likelihood of invasive cancer is very low in small cysts raise the possibility of management with careful observation in asymptomatic patients. Patients with branch duct IPMNs who are symptomatic should be treated with resection not only to alleviate the symptoms, but also because of a higher likelihood of malignancy. It is important to emphasize that the decision to treat should be individualized and based on patient preferences and willingness or unwillingness to undergo follow-up studies, as well as on the availability of safe pancreatic resection. Moreover, more data based on pathological studies of branch duct IPMNs >30 mm and without main duct dilation or mural nodules are needed to determine if all branch duct IPMNs >30 mm in size should be resected immediately.

3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?

Unless there are contraindications for operation, all MCNs should be resected. Usually these neoplasms are localized in the body-tail of the gland and affect middle-aged women [29, 35, 36]. Current thinking is that all MCNs may progress to malignancy, and the life expectancy of most of these patients will allow development of mucinous cystadenocarcinoma, which has a very low resectability and a very poor prognosis [35, 36]. Furthermore, the operation, usually a left pancreatectomy, has a low morbidity and practically no mortality [51]. Predictors of malignancy such as large size, mural nodules, and eggshell calcification [32] mean only that spleen preserving techniques, either laparoscopically or open, must be avoided in order to obtain a correct oncological lymph node dissection [52–55].

4. Method of Resection

4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?

It is not always easy to assess pre- and intraoperatively the grade of invasiveness [56]. Whenever any doubt exists, a typical resection (pancreatoduodenectomy, left pancreatectomy, total pancreatectomy according to the site and the extension of the disease) with lymph node dissection must be pursued [34, 57]. In very limited size lesions, without any laboratory, clinical or radiological

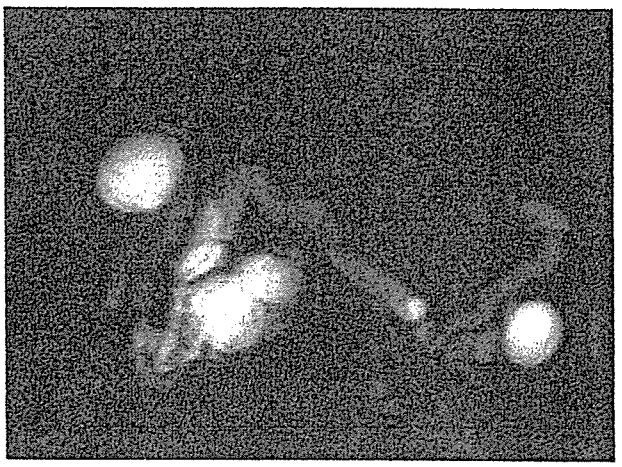

Fig. 9. MRCP outlining two branch duct IPMNs in the head and tail of the pancreas in the same patient as shown in figure 4.

suspicion of malignancy, limited resections can be planned, but should always be contingent on a careful intraoperative final assessment.

4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?

The aim of limited pancreatic resection is to preserve exocrine and endocrine pancreatic functions. Newer understanding of surgical anatomy of the pancreas has led to the proposal of various types of limited pancreatectomy [58, 59]. However, limited pancreatectomy has its problems, including technical difficulty (mostly related to a complicated surgical anatomy), a higher incidence of postoperative complications including pancreatic fistulae, and the risk of recurrence from potentially residual neoplasm. For pancreatic head lesions, duodenum-preserving pancreas head resection [60–62], pancreatic head resection with second portion duodenectomy [63], ventral pancreatectomy [64], resection of uncinate process [65], and ductal branch-oriented minimal pancreatectomy [66] have been proposed, for pancreatic body diseases, a dorsal pancreatectomy [67] and middle segmentectomy [68, 69], and for pancreatic tail neoplasms, spleen-preserving distal pancreatectomy [52–54]. Branch duct IPMNs with possible in-situ carcinoma and MCNs can be candidates for limited pancreatectomy as far as negative ductal margins can be obtained and safe pancreatectomy can be performed but no good follow-up data on recurrence are available.

4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?

Branch duct IPMNs can often be multifocal and located in distant segments of the pancreas (fig. 9). This is especially evident when EUS or MRCP is performed. It is unclear if multifocality confers a higher risk of invasive cancer than that predicted by the cyst size alone. If there is an indication for surgical resection (i.e., the patient is symptomatic, or the lesions are >3 cm and/or have mural nodules), a decision to proceed with a total pancreatectomy in order to remove all the lesions must be weighed carefully against the ability of the patient to manage the metabolic consequences of an apancreatic state. The age of the patient plays an important role in this decision, since the longer the life expectancy, the greater the risk of development of invasive cancer. While some studies have suggested a time lag of 5–7 years between adenomas and carcinomas (based on age differences of resected patients with benign and malignant IPMNs) [23, 24], in reality there is practically no information on the natural history of branch duct IPMNs, and it may be equally reasonable to resect the dominant lesion and observe the remainder until they become symptomatic or growth is documented.

5. Histological Questions

5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?

The role of frozen section for MCNs is somewhat different from that for IPMNs:

Frozen Section for IPMNs

Frozen section of the surgical margins has an important role in the intraoperative management of IPMNs. Microscopic extension of the neoplastic cells beyond the grossly (radiologically and macroscopically) visible boundaries of the main lesion is a common occurrence in IPMNs, and this often needs to be investigated by performing a frozen section.

Caution should be exercised in interpreting the frozen section result, keeping in mind the following concerns:

(1) It should be remembered that even a negative margin does not assure the absence of neoplastic cells in the remaining pancreas. It has been well documented that IPMNs can be multifocal, and that there are sometimes 'skip' lesions in IPMNs, with non-neoplastic tissue intervening neoplastic foci. Along similar lines, there is also evidence that IPMNs may, in some instances, be a marker of invasive carcinoma [70]. This is exemplified by the cases that have an IPMN in the pancreatic head and a seemingly independent invasive ductal carcinoma in the tail of the organ. In other words, in some patients, IPMN may be a marker of a field defect and propensity for cancer formation in the pancreas, in some cases, away from the IPMN itself. Therefore, every effort should be made, preoperatively and intraoperatively, to rule out the presence of the neoplasm in the remaining pancreas. Furthermore, it has been well documented that a third of the IPMN patients have a separate malignancy in other organs [71, 72].

(2) It should also be remembered that grading of IPMNs can be subjective, and frozen tissue exhibit artifacts that accentuate the difficulty in interpretation of the histomorphologic findings. The decision to resect additional pancreatic parenchyma should be individualized and based on careful discussion between the surgeon and pathologist. A problem commonly encountered is denuded epithelium, where evaluation of the margin becomes impossible. To avoid this, gentle handling of the tissue (both in the operating room and the laboratory) is necessary. Stepwise sections of the tissue in the laboratory or even re-melting and re-embedding the reverse side of the tissue (i.e., if the fragment has not been oriented) may be considered.

Management of Positive Margins in IPMNs

The relative risk and biologic significance of various grades and subsets of IPMNs have not yet been fully established. However, the following assumptions can be made based on the current data in the literature:

IPM Adenoma. It is generally believed that IPM adenomas do not warrant further resection. This impression mostly stems from the fact that most branch duct IPMNs have been successfully followed up for decades, and only rarely developed invasive cancer. These branch duct IPMNs are typically adenomas (with no cytoarchitectural atypia) and have gastric/foveolar type epithelium, the type that used to be classified as 'IPMT (intraductal papillary-mucinous tumor) hyperplasia' in the JPS classification system [48, 73]. Whether these represent hyperplasia or adenoma is a discussion beyond the scope of this article. Regardless of the term, it is generally believed that such lesions bear only minimal risk of progression to cancer, which warrants close follow-up of the patient but does not justify (further) operation. Along the same lines, if a coincidental low-grade PanIN (1 and 2) is encountered in a resection margin, it is believed that no further resection is necessary. This impression is based on the fact that PanIN-1 and -2 are common incidental findings in the general population [40, 74].

IPMN with Borderline Atypia. This category is difficult to characterize and hence its management decision is also difficult. Not surprisingly, some of these borderline lesions are closer to adenomas and hence assumed to be less clinically significant and may not require further resection. On the other hand, those that have florid papilla formation (with villous-intestinal or pancreatobiliary patterns) may warrant further attention [75]. Typically, if there are florid papillary nodules at the margin, there are a lot more papillary nodules in the remaining pancreas, some of which prove to have higher-grade dysplasia in further examination. Therefore, such lesions may require further resection, if clinically indicated.

IPMN with CIS or Invasive Carcinoma. The relative risk of 'progression' and fatal outcome in IPMNs is difficult to calculate. Even patients with tubular type invasive carcinoma arising in IPMNs sometimes experience a more protracted clinical course than those with conventional ductal adenocarcinoma of this organ. Nevertheless, there is general consensus that IPMNs with CIS or invasive carcinoma are potentially fatal diseases if left untreated, and ought to be completely resected whenever feasible. To a lesser degree, the same may also apply to PanIN-3, which may be coincidentally encountered in patients with IPMN [76]. It should be noted that in some patients with IPMNs, it is difficult to determine whether some of the neoplastic changes within the small ducts represent PanINs or IPMNs [40, 77, 78]. At this point, this question is more an academic exercise than a practical issue, because, if such a lesion is encountered at the margin, the management should be based on the degree of cytologic atypia, and if frank CIS is noted, further resection may be attempted, if clinically indicated.

Frozen Section for MCNs

For MCNs, the role of frozen section appears to be more limited. Typically, MCNs have thick-walled cysts and their boundaries are easily discernible. The vast majority forms a localized mass in the tail or body, and unlike in IPMNs, microscopic extension of the lesion into the seemingly uninvolved pancreas is very uncommon. However, frozen section is indicated to rule out invasive

carcinoma, in particular, if a dubious firmness is close to the resection margin. If invasive carcinoma is detected at the margin, it ought to be treated as any other invasive carcinoma of this organ. Rarely, an incidental PanIN may also be detected at the margin. As discussed previously, PanIN-1 and -2 are common incidental findings, including in pancreata with MCNs [74, 79]. These are generally regarded as clinically inconsequential. Coincidental PanIN-3, on the other hand, is exceedingly uncommon in the absence of ductal adenocarcinoma. If encountered at the margin, PanIN-3 may require further attention.

5b. Are there special instructions for specimen processing in MCNs and IPMNs?

In IPMNs and MCNs, in-situ and invasive carcinoma may be multifocal and macroscopically (grossly) invisible. Therefore, it is not possible to rule out the presence of carcinoma unless the neoplasm is examined thoroughly. This is probably the main reason for the discrepancy in the literature regarding the value of grade (classification as adenoma, borderline, CIS, etc.) in these neoplasms [26, 30, 36]. It appears that undergrading due to undersampling is possibly the main reason for the 'unexpectedly' aggressive clinical course of some lower-grade examples of IPMNs and MCNs. Accordingly, some authors advocate pathologic sampling of the entire neoplasm [36, 40].

5c. Are there special instructions for specimen processing to differentiate branch duct from main duct IPMNs?

Once the neoplasm is resected and examined pathologically, the significance of classifying an IPMN as branch duct vs. main duct type is largely overridden by the other pathologic parameters such as the presence, type and extent of invasive carcinoma or grading of the IPMN component. Nevertheless, there is some evidence that branch duct IPMN may be a distinct subset, and it is suggested that the pathologists make every attempt to classify the process as branch duct or main duct type by documenting the distribution of the lesion in the ductal system. There are no special instructions for specimen processing for this purpose. However, it should be kept in mind that there are no reliable histological features to distinguish main ducts from the branch ducts in the pancreas by microscopic examination alone, especially when the duct is dilated by IPMN. Therefore, careful dissection of the specimen and proper identification of the main duct in the sections guide (either in a text form or by a diagram) is imperative in documenting the findings in the main duct. There are different approaches to dissection of these specimens, and the Japanese approach is well described in the textbook [80]. Taking a photo and a photocopy of the gross cut sections makes it easy to compare the relationships between the lesion and the main and/or branch duct.

6. Method of Follow-Up

6a. How should patients with non-resected IPMN and MCN be followed? How often should they be followed and which techniques should be employed as baseline investigations?

The decision to follow rather than resect a pancreatic cystic lesion is a matter of clinical judgment based on the age of the patient, comorbidities, and estimation of the cancer risk in the lesion. It is clear that the risk of prevalent cancer is high in main duct IPMN (table 2). Although this has not been formally studied, a review of studies on branch duct IPMN suggests that the prevalence of invasive cancer may be high (up to 30%) in symptomatic branch duct IPMN and low (0–5%) in those with asymptomatic branch duct IPMN. There are few reports in the English literature on identifying predictors of malignancy in asymptomatic mucinous lesions [22]. There have been four reports in the English literature describing the natural history of pancreatic IPMN evaluated by ERCP, CT or MRCP [81–84].

Based on limited available data from these studies it appears that asymptomatic cystic lesions without main duct dilation (>6 mm), those without mural nodules, and those <30 mm in size have a low risk of prevalent cancer and a low risk of progressing to invasive cancer in near-term (12- to 36-month) follow-up.

Ideally the imaging modality at baseline and follow-up should provide adequate information regarding the size of the lesion, size of the main pancreatic duct, and presence of intramural nodules. At least the first two criteria can be assessed satisfactorily by using non-invasive imaging studies such as multidetector high-resolution CT or MRCP, or by more invasive tests such as EUS. Assessment for intramural nodules requires EUS. Transabdominal ultrasonography is useful for follow-up in thin patients with clearly visualized cysts.

The interval between follow-up examinations remains to be determined. However, until definitive studies are performed to answer this question, it would appear reasonable to do yearly follow-up if lesion is <10 mm in size, 6–12 monthly follow-up for lesions between 10 and 20 mm, and 3–6 monthly follow-up for lesions >20 mm

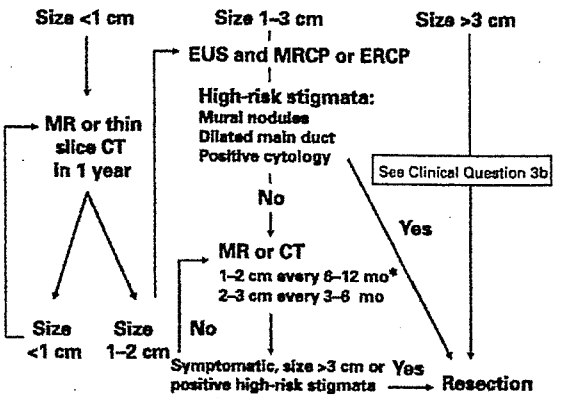

Fig. 10. Algorithm for the management of branch duct IPMN. * The interval of follow-up can be lengthened after 2 years of no change.

(fig. 10). On follow-up studies, appearance of symptoms attributable to the cyst (e.g., pancreatitis), presence of intramural nodules, cyst size >30 mm, dilation of the main pancreatic duct (>6 mm) would be indications for resection. The interval of follow-up can be lengthened after 2 years of no change.

6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?

Patients with resected benign MCNs do not need follow-up, since several studies have shown that the risk of recurrence following resection is nil [29, 35]. Patients with resected malignant MCNs do have a significant risk of recurrence, and should be followed up every 6 months regarding local recurrence and distant metastasis (mainly hematogenous) using either CT or MRI. Patients with resected benign IPMNs do have a risk of recurrence in the remaining pancreas, and if it occurs can benefit from further resection. The frequency of this event and its relationship to surgical margins (i.e., positive, negative or indeterminate) is not clear, since most series thus far have had relatively short median follow-up, but seems to be at least 7% in non-invasive IPMN [23, 24, 40]. There is no evidence in the literature to define the frequency and type of surveillance that is required to detect these recurrences. One study suggests only clinical follow-up, and imaging if symptoms appear [40], but it is not clear if imaging in absence of symptoms could be beneficial by detecting earlier lesions. It may be reasonable to get yearly follow-up with CT or MRI, and then space this interval if no changes have occurred over several years. Patients with invasive IPMNs do have a significant risk of recurrence, and probably should be evaluated every 6 months. Serum levels of CEA and CA19-9 have no proven value in the follow-up of these patients, and if obtained it should be done for the purposes of research.

6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?

There have been several reports in the English literature describing the high prevalence of malignant neoplasms in patients with IPMNs but not in those with MCNs. Yamaguchi et al. [85] reported that 27% of 48 patients with IPMNs had synchronous or metachronous malignant neoplasms in the stomach, colon, rectum, lung, breast, liver, but only in 5% of 21 patients with MCNs. Sugiyama and Atomi [71] also documented that 32% of 42 patients with IPMNs developed extrapancreatic malignant neoplasms. Adsay et al. [72] found a history of another malignancy in 29% or 8 of 28 patients with IPMNs. Osanai et al. [86] gave a 24% prevalence of extrapancreatic malignancies in a large series of 148 patients with IPMNs. Furthermore, Yamaguchi et al. [70] reported synchronous or metachronous occurrence of pancreatic cancer of ordinary type in the pancreas harboring IPMNs. Although there is not yet definitive evidence, care should be taken to the possible occurrence of malignant neoplasms in the pancreas and other organs in patients with IPMNs on follow-up.